

CLAIMS

1. Use of tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate, and at least one multi-targeting antifolate, for the manufacture
5 of a pharmaceutical composition for the treatment of cancer.

2. Use according to claim 1, wherein at least 60% by weight of said THF, methyl-THF and/or methylene-THF is in the form of a biologically active isomer.

10 3. Use according to claim 1 or 2, wherein said multi-targeting antifolate is selected from the group consisting of premetrexed, raltitrexed, and lometrexol.

4. Use according to any one of the preceding claims, wherein said pharmaceutical composition further comprises
15 at least one chemotherapeutic agent selected from the group consisting of anthracyclines, platinum derivatives, topoisomerase inhibitors, and antimetabolites.

5. Use according to any one of the preceding claims, wherein said tetrahydrofolate, methylene-tetrahydrofolate
20 and/or methyl-tetrahydrofolate, and said at least one multi-targeting antifolate, are formulated in different pharmaceutical compositions.

6. Use according to any one of the claims 1-4, wherein said tetrahydrofolate, methylene-tetrahydrofolate
25 and/or methyl-tetrahydrofolate, and said at least one multi-targeting antifolate, are formulated in a common pharmaceutical composition.

7. Use according to any one of the preceding claims wherein said cancer is selected from the group consisting
30 of breast cancer, gastric cancer, gall bladder cancer, bile duct cancer, colon cancer, rectal cancer, liver cancer, pancreatic cancer, head and neck cancer, and mesothelioma cancer.

8. A pharmaceutical composition comprising tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate, and at least one multi-targeting antifolate.
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9. A pharmaceutical composition according to claim 8, wherein at least 60% by weight of said THF, methyl-THF and/or methylene-THF is in the form of a biologically active isomer.

5 10. A pharmaceutical composition according to claim 8 or 9, wherein said multi-targeting antifolate is selected from the group consisting of premetrexed, raltitrexed, and lometrexol.

10 11. A pharmaceutical composition according to any one of the claims 8 to 10, further comprising at least one chemotherapeutic agent selected from the group consisting of anthracyclines, platinum derivatives, topoisomerase inhibitors, and antimetabolites.

15 12. A pharmaceutical composition according to any one of the claims 8 to 11, wherein said tetrahydrofolate, said methylene-tetrahydrofolate and/or said methyl-tetrahydrofolate, and said at least one multi-targeting antifolate, are formulated in different pharmaceutical compositions.

20 13. A pharmaceutical composition according to any one of the claims 8 to 11, wherein said tetrahydrofolate, said methylene-tetrahydrofolate and/or said methyl-tetrahydrofolate, and said at least one multi-targeting antifolate, are formulated in a common pharmaceutical
25 composition.

30 14. A kit comprising a pharmaceutical composition comprising tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate, and a pharmaceutical composition comprising at least one multi-targeting antifolate.

15. A kit according to claim 14, wherein at least 60% by weight of said tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate is in the form of a biologically active isomer.

35 16. A kit according to claim 14 or 15, further comprising a pharmaceutical composition comprising at least one chemotherapeutic agent selected from the group con-

sisting of anthracyclines, platinum derivatives, topoisomerase inhibitors, and antimetabolites.

17. A method for the treatment of cancer comprising administering to a patient a pharmaceutically active
5 amount of tetrahydrofolate, methylene-tetrahydrofolate and/or methyl-tetrahydrofolate, and a pharmaceutically active amount of at least one multi-targeting antifolate.

18. A method according to claim 17, wherein at least 60% by weight of said tetrahydrofolate, methylene-
10 tetrahydrofolate and/or methyl-tetrahydrofolate is in the form of a biologically active isomer.

19. A method according to claim 17 or 18, wherein said multi-targeting antifolate is selected from the group consisting of premetrexed, raltitrexed, and
15 lometrexol.

20. A method according to any one of the claims 17 to 19, further comprising administering a pharmaceutically active amount of a chemotherapeutic agent selected from the group consisting of anthracyclines, platinum derivatives, topoisomerase inhibitors, and antimetabolites.
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21. A method according to any one of the claims 17-20, wherein said tetrahydrofolate, said methylene-tetrahydrofolate and/or said methyl-tetrahydrofolate, and said at least one multi-targeting antifolate, are administered consecutively.
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22. A method according to any one of the claims 17 to 20, wherein said tetrahydrofolate, said methylene-tetrahydrofolate and/or said methyl-tetrahydrofolate, and said at least one multi-targeting antifolate, are administered simultaneously.
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23. A method according to any one of the claims 17 to 22, wherein said cancer is selected from the group consisting of breast cancer, gastric cancer, gall bladder cancer, bile duct cancer, colon cancer, rectal cancer, liver cancer, pancreatic cancer, head and neck cancer, and mesothelioma cancer.
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